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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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R C van Dijk



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If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

3-Aryl-2-cyano-3-hydroxy-acrylic acid derivatives

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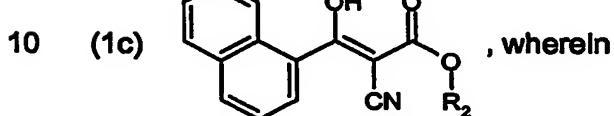
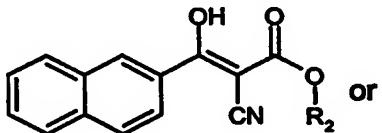
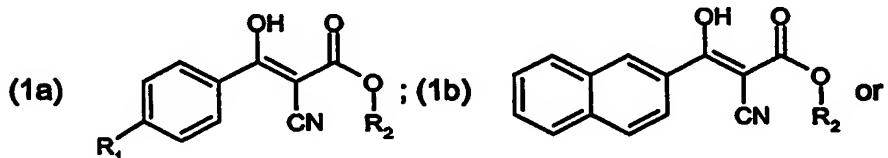
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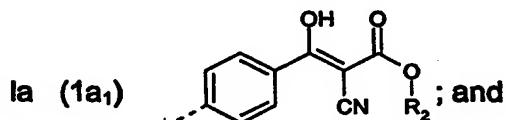
3-Aryl-2-cyano-3-hydroxy-acrylic acid derivatives

The present invention relates to selected 3-aryl-2-cyano-3-hydroxy-acrylic acid derivatives, the preparation of these compounds, and to the use of such compounds in the antimicrobial treatment of surfaces, as antimicrobial active substances against gram-positive and gram-negative bacteria, yeasts and fungi and also in the preservation of cosmetics, household products, textiles and plastics and for use in disinfectants.

The present invention relates to 3-aryl-2-cyano-3-hydroxy-acrylic acid derivatives of formula



R₁ is hydrogen, C₁-C₂₀alkyl; C₁-C₂₀alkoxy; CF₃; C₆-C₁₀aryl; or a radical of formu-



R₂ is hydrogen; or C₁-C₂₀alkyl.

- 15 C₁-C₂₀alkyl are straight-chain or branched alkyl radicals like methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.butyl, tert.butyl, amyl, isoamyl or tert.amyl, hexyl, 2-ethylhexyl, heptyl, octyl, isooctyl, nonyl, decyl, undecyl, dodecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl oder eicosyl.
- 20 C₁-C₂₀alkoxy are for example z.B. Methoxy, Ethoxy, n-Propoxy, Isopropoxy, n-Butoxy, sek.Butoxy, tert. Butoxy, Amyloxy, Isoamyloxy oder tert.Amyloxy, Hexyloxy, Heptyloxy, Octyloxy, Isooctyloxy, Nonyloxy, Decyloxy, Undecyloxy, Dodecyloxy, Tetradecyloxy, Pentadecyloxy, Hexadecyloxy, Heptadecyloxy oder Octadecyloxy.

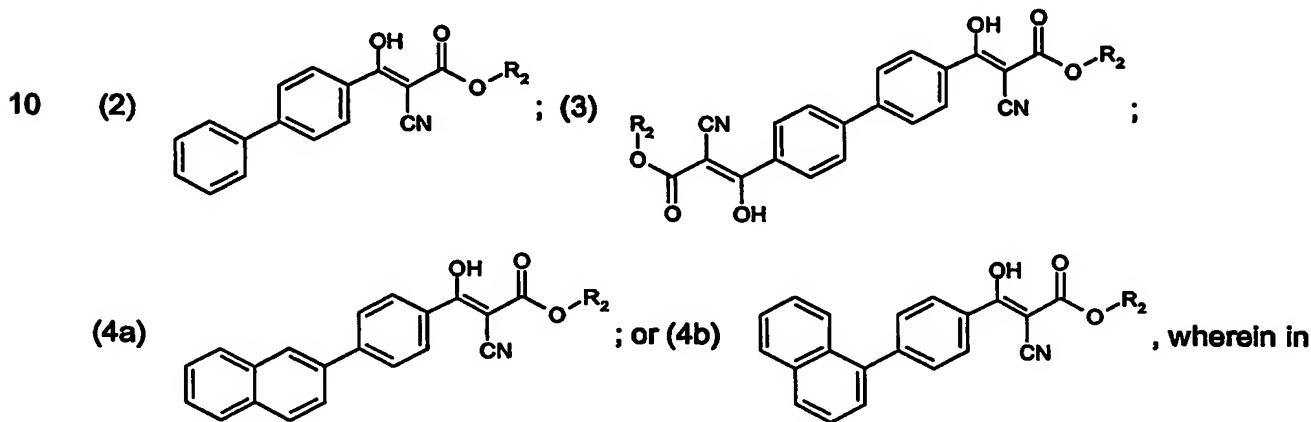
C₆-C₁₀aryl is for example naphthyl and preferably phenyl.

In accordance with the invention, preference is given to compounds of formula (1a), wherein R₁ is C₆-C₁₀aryl, and most preferably phenyl.

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Preference is given to compounds of formula (1a), (1b) or (1c), wherein R₂ C₁-C₂₀-Alkyl.

Very special preference is given to compounds of formulae

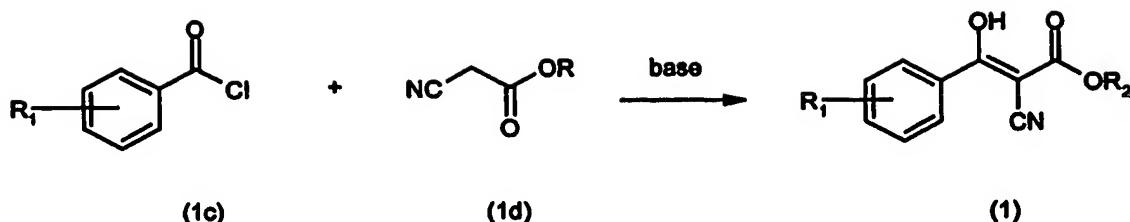


the formulas (2) to (5)

R₂ is C₁-C₂₀alkyl.

15 The preparation of the 3-aryl-2-cyano-3-hydroxy-acrylic acid derivatives can be carried out according to known methods.

For the preparation of the acrylic acid derivatives of the general formula (1a) of the corresponding cyanoacetates of the formula (1d) are condensed with carbon acid chlorides 20 of the formula (1c) at temperatures from -100°C to +100°C, preferably at -80°C, in a suitable solvent, like diethylether or tetrahydrofuran in the presence of a base like metal alkoholates, metal silicides or metal amides, preferably lithium diisopropylamide according to the following reaction scheme:



R₁ and R₂ are defined as given in formula (1a), (1b) or (1c).

The process for the preparation of the 3-aryl-2-cyano-3-hydroxy-acrylic acid derivates is a
5 further object of the present invention.

The 3-aryl-2-cyano-3-hydroxy-acrylic acid derivatives of the present Invention exhibit pro-
nounced antimicrobial action, especially against pathogenic gram-positive and gram-negative
bacteria and against bacteria of the skin flora, and also against yeasts and moulds. They are
10 accordingly suitable especially for disinfection, deodorisation, and for general and antimicro-
bial treatment of the skin and mucosa and of integumentary appendages (hair), more espe-
cially for the disinfection of hands and wounds.

They are accordingly suitable as antimicrobial active substances and preservatives in per-
15 sonal care preparations such as, for example, shampoos, bath additives, haircare prepara-
tions, liquid and solid soaps (based on synthetic surfactants and salts of saturated and/or un-
saturated fatty acids), lotions and creams, deodorants, other aqueous or alcoholic solutions,
e.g. cleansing solutions for the skin, moist cleaning cloths, oils or powders.

20 The invention accordingly relates also to a personal care preparation comprising at least one
compound of formula (1a), (1b) or (1c) and cosmetically tolerable carriers or adjuvants.

The personal care preparation according to the invention contains from 0.01 to 15 % by
weight, preferably from 0.1 to 10 % by weight, based on the total weight of the composition,
25 of a compound of formula (1a), (1b) or (1c), and cosmetically tolerable adjuvants.

Depending upon the form of the personal care preparation, it comprises, in addition to the 3-
aryl-2-cyano-3-hydroxy-acrylic acid derivatives of formula (1a), (1b) or (1c), further constitu-
ents such as, for example, sequestering agents, colorants, perfume oils, thickeners or solidifi-
30 fiers (consistency regulators), emollients, UV-absorbers, skin protective agents, antioxidants,

additives that improve the mechanical properties, such as dicarboxylic acids and/or aluminum, zinc, calcium or magnesium salts of C₁₄-C₂₂fatty acids, and, optionally, preservatives.

The personal care preparation according to the invention may be in the form of a water-in-oil

- 5 or oil-in-water emulsion, an alcoholic or alcohol-containing formulation, a vesicular dispersion of an ionic or non-ionic amphiphilic lipid, a gel, a solid stick or an aerosol formulation.

As a water-in-oil or oil-in-water emulsion, the cosmetically tolerable adjuvant contains preferably from 5 to 50 % of an oil phase, from 5 to 20 % of an emulsifier and from 30 to 90 %

- 10 water. The oil phase may comprise any oil suitable for cosmetic formulations such as, for example, one or more hydrocarbon oils, a wax, a natural oil, a silicone oil, a fatty acid ester or a fatty alcohol. Preferred mono- or poly-ols are ethanol, isopropanol, propylene glycol, hexylene glycol, glycerol and sorbitol.

- 15 Cosmetic formulations according to the invention are used in various fields. There come into consideration, for example, especially the following preparations:

- skin-care preparations, e.g. skin-washing and cleansing preparations in the form of tablet-form or liquid soaps, synthetic detergents or washing pastes;
- bath preparations, e.g. liquid (foam baths, milks, shower preparations) or solid bath preparations, e.g. bath cubes and bath salts;
- skin-care preparations, e.g. skin emulsions, multi-emulsions or skin oils;
- cosmetic personal care preparations, e.g. facial make-up in the form of day creams or powder creams, face powder (loose or pressed), rouge or cream make-up, eye-care preparations, e.g. eyeshadow preparations, mascaras, eyeliners, eye creams or eye-fix creams; lip-care preparations, e.g. lipsticks, lip gloss, lip contour pencils, nail-care preparations, such as nail varnish, nail varnish removers, nail hardeners or cuticle removers;
- intimate hygiene preparations, e.g. intimate washing lotions or intimate sprays;
- foot-care preparations, e.g. foot baths, foot powders, foot creams or foot balsams, special deodorants and antiperspirants or callus-removing preparations;
- light-protective preparations, such as sun milks, lotions, creams or oils, sun-blocks or tropicals, pre-tanning preparations or after-sun preparations;
- skin-tanning preparations, e.g. self-tanning creams;
- depigmenting preparations, e.g. preparations for bleaching the skin or skin-lightening preparations;

- insect-repellents, e.g. insect-repellent oils, lotions, sprays or sticks;
 - deodorants, such as deodorant sprays, pump-action sprays, deodorant gels, sticks or roll-ons;
 - antiperspirants, e.g. antiperspirant sticks, creams or roll-ons;
- 5 - preparations for cleansing and caring for blemished skin, e.g. synthetic detergents (solid or liquid), peeling or scrub preparations or peeling masks;
- hair-removal preparations in chemical form (depilation), e.g. hair-removing powders, liquid hair-removing preparations, cream- or paste-form hair-removing preparations, hair-removing preparations in gel form or aerosol foams;
- 10 - shaving preparations, e.g. shaving soap, foaming shaving creams, non-foaming shaving creams, foams and gels, preshave preparations for dry shaving, aftershaves or after-shave lotions;
- fragrance preparations, e.g. fragrances (eau de Cologne, eau de toilette, eau de parfum, parfum de toilette, perfume), perfume oils or perfume creams;
- 15 - dental care, denture-care and mouth-care preparations, e.g. toothpastes, gel toothpastes, tooth powders, mouthwash concentrates, anti-plaque mouthwashes, denture cleaners or denture fixatives;
- cosmetic hair-treatment preparations, e.g. hair-washing preparations in the form of shampoos and conditioners, hair-care preparations, e.g. pretreatment preparations, hair tonics, styling creams, styling gels, pomades, hair rinses, treatment packs, intensive hair treatments, hair-structuring preparations, e.g. hair-waving preparations for permanent waves (hot wave, mild wave, cold wave), hair-straightening preparations, liquid hair-setting preparations, hair foams, hairsprays, bleaching preparations, e.g. hydrogen peroxide solutions, lightening shampoos, bleaching creams, bleaching powders, bleaching pastes or oils, temporary, semi-permanent or permanent hair colorants, preparations containing self-oxidising dyes, or natural hair colorants, such as henna or camomile.

An antimicrobial soap has, for example, the following composition:

0.01 to 5 % by weight of a compound of formula (1a), (1b) or (1c),

30 0.3 to 1 % by weight titanium dioxide,

1 to 10 % by weight stearic acid,

soap base ad 100 %, e.g. a sodium salt of tallow fatty acid or coconut fatty acid, or glycerol.

A shampoo has, for example, the following composition:

0.01 to 5 % by weight of a compound of formula (1a), (1b) or (1c),

12.0 % by weight sodium laureth-2-sulfate,

4.0 % by weight cocamidopropyl betaine,

3.0 % by weight NaCl and

5 water ad 100 %.

A deodorant has, for example, the following composition:

0.01 to 5 % by weight of a compound of formula (1a), (1b) or (1c),

60 % by weight ethanol,

10 0.3 % by weight perfume oil, and

water ad 100 %.

The invention relates also to an oral composition containing from 0.01 to 15 % by weight,

based on the total weight of the composition, of a compound of formula (1a), (1b) or (1c), and

15 orally tolerable adjuvants.

Example of an oral composition:

10 % by weight sorbitol,

10 % by weight glycerol,

20 15 % by weight ethanol,

15 % by weight propylene glycol,

0.5 % by weight sodium lauryl sulfate,

0.25 % by weight sodium methylcocoyl taurate,

0.25 % by weight polyoxypropylene/polyoxyethylene block copolymer,

25 0.10 % by weight peppermint flavouring,

0.1 to 0.5 % by weight of a compound of formula (1a), (1b) or (1c), and

48.6 % by weight water.

The oral composition according to the invention may be, for example, in the form of a gel, a

30 paste, a cream or an aqueous preparation (mouthwash).

The oral composition according to the invention may also comprise compounds that release fluoride ions which are effective against the formation of caries, for example inorganic fluo-

ride salts, e.g. sodium, potassium, ammonium or calcium fluoride, or organic fluoride salts, e.g. amine fluorides, which are known under the trade name Olafluor.

3-Aryl-2-cyano-3-hydroxy-acrylic acid derivatives of formulae (1a), (1b) or (1c) according to
5 the invention are also suitable for treating, especially preserving, textile fibre materials. Such
materials are undyed and dyed or printed fibre materials, for example of silk, wool, polyamide
or polyurethanes, and especially cellulosic fibre materials of all kinds. Such fibre materials
are, for example, natural cellulose fibres, such as cotton, linen, jute and hemp, as well as
10 cellulose and regenerated cellulose. Preferred suitable textile fibre materials are made of
cotton.

3-aryl-2-cyano-3-hydroxy-acrylic acid derivatives according to the invention are suitable also
for treating, especially imparting antimicrobial properties to or preserving, plastics such as,
for example, polyethylene, polypropylene, polyurethane, polyester, polyamide, polycarbon-
ate, latex etc.. Fields of use therefor are, for example, floor coverings, plastics coatings, plas-
15 tics containers and packaging materials; kitchen and bathroom utensils (e.g. brushes,
shower curtains, sponges, bathmats), latex, filter materials (air and water filters), plastics ar-
ticles used in the field of medicine such as, for example, dressing materials, syringes, cathe-
ters etc., so-called "medical devices", gloves and mattresses.

20 Paper, for example papers used for hygiene purposes, may also be provided with antimicro-
bial properties using the 4-aminopyrimidines according to the invention.

It is also possible for nonwovens such as, for example, nappies/diapers, sanitary towels,
panty liners, and cloths for hygiene and household uses, to be provided with antimicrobial
25 properties in accordance with the invention.

The 3-aryl-2-cyano-3-hydroxy-acrylic acid derivatives of formulae (1a), (1b) or (1c) are also
used in washing and cleaning formulations such as, for example, liquid or powder washing
agents or softeners.

30 The 3-aryl-2-cyano-3-hydroxy-acrylic acid derivatives of formulae (1a), (1b) or (1c) can also
be used especially in household and general-purpose cleaners for cleaning and disinfecting
hard surfaces.

A cleaning preparation has, for example, the following composition:

0.01 to 5 % of a compound of formula (1a), (1b) or (1c),

3.0 % octyl alcohol 4EO,

1.3 % fatty alcohol C₈-C₁₀polyglucoside,

5 3.0 % isopropanol, and

water ad 100 %.

In addition to preserving cosmetic and household products, the preservation of technical

products, the provision of technical products with antimicrobial properties and use as a bio-

10 cide in technical processes are also possible, for example in paper treatment, especially in paper treatment liquors, printing thickeners of starch or cellulose derivatives, surface-coatings and paints.

The 3-aryl-2-cyano-3-hydroxy-acrylic acid derivatives of formulae (1a), (1b) or (1c) are also

15 suitable for the antimicrobial treatment of wood and for the antimicrobial treatment of leather, the preserving of leather and the provision of leather with antimicrobial properties.

The compounds according to the invention are also suitable for the protection of cosmetic products and household products from microbial damage.

20 sich die erfindungsgemäßen Verbindungen zum Schutz von kosmetischen Produkten und Haushaltsprodukten vor mikrobieller Verderbnis.

Furthermore, the compounds of the present invention are able to penetrate biofilms formed on animated and inanimated surfaces. They can also, if necessary, prevent the adhesion of

25 bacteria on surfaces and the further forming of the biofilmes. They are able to detach the biofilm and/or to inhibit the groth of the biofilm forming microorganisms in the biological matrix or to kill them.

Generally, biofilms are aggregates of animated or inanimated microorganisms, preferably

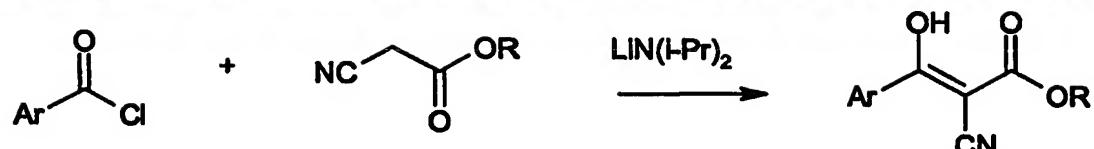
30 bacteria, togehter with their intermediate catabolic products in form of extracellular polymer substances (EPS-matrix), like polysaccharides. The efficacy of antimicrobial actives, which normally show a distinct growth-inhibition or killing activity against plankton cells, may strongly be reduced for microorganisms, which are organized in biofilms, i.e. becaususe of insufficient penetration of the active into the biomatrix.

The compounds of the present invention are therefore effective actives against biofilms which are formed on the surface of teeth and oral mucosa, which are participated in the formation of degenerative diseases in the oral region, like caries or periodontosis.

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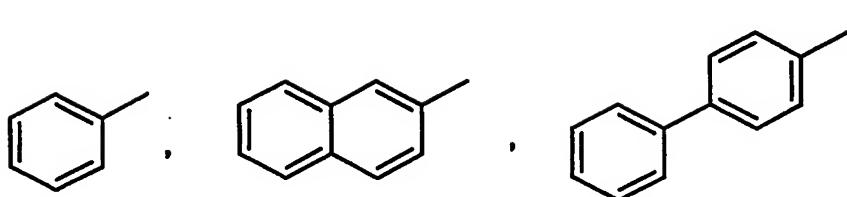
The following Examples illustrate, but do not limit, the present invention.

Example 1: Preparation of aryl-mono-(2-cyano-3-hydroxy-acrylic acid)-ester (101):



(101)

Ar =



R = iso-butyl, n-butyl, iso-propyl, n-octyl, iso-octyl

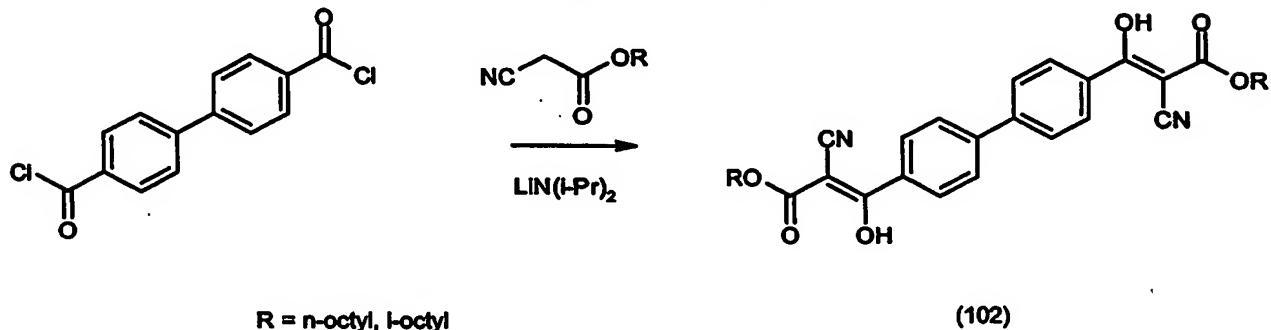
- A 1.6 m solution of 1 mmol n-BuLi in hexane is added to a solution of 1 mmol diisopropylamine in THF_{abs} (6 ml / ml diisopropylamine) at -10°C. The mixture is stirred for 15 min. and than cooled down to -78°C.
- After that the solution of 0.5 mmol of the corresponding cyano acetate is added in THF (1ml / g cyanoacetate) at this temperature initially, additionally stirred for 15 min and than the solution of 0.5 mmol of the acid chloride is added in THF (2 ml / g acid chloride).
- 5 After stirring of 45 min at -78°C the reaction mixture is quenched at this temperature with 15 % HCl und warmed up to room temperature over night.
- For working up the reaction mass is extracted with acetic acid ester, the organic phase is washed with water for several times, dried and purified and concentrated.
- 10 The product is isolated and purified via chromatographic methods on silica gel (acidic acid ester /hexane 10/1).
- 15

The following derivatives are obtained with this method:

	Ar	R	Yield [%]
(101a)	4-biphenyl	i-propyl	37
(101b)	4-biphenyl	n-butyl	25

	<u>Ar</u>	<u>R</u>	<u>Yield [%]</u>
(101c)	4-biphenyl	i-butyl	18
(101d)	4-biphenyl	n-octyl	23
(101e)	4-biphenyl	i-octyl	22
(101f)	2-naphthyl	n-octyl	20

Example 2: Preparation of aryl-bis-(2-cyano-3-hydroxy-acrylic acid) ester (102):



5

A 1.6 m solution mmol of n-BuLi in hexane is added at -10°C to a solution of 1 mmol diisopropylamine in THF_{abs} (6 ml / ml diisopropylamine). The mixture is stirred for 15 min. and than cooled down to -78°C.

10 After that the solution of 0.5 mmol of the corresponding cyano acetate is added in THF (1ml / g cyanoacetate) at this temperature initially, additionally stirred for 15 min and than the solution of 0.5 mmol of the acid chloride is added in THF (2 ml / g acid chloride).

After stirring of 45 min at -78°C the reaction mixture is quenched at this temperature with 15 % HCl und warmed up to room temperature over night.

15 The working up for reconditioning, isolation and purification is carried out according to example 1.

The following derivatives are obtained with this method:

	<u>R</u>	<u>Yield [%]</u>
(102a)	n-octyl	13
(102b)	i-octyl	21

Table 1: 1H-NMR data of the compounds:

	<u>compound</u>	<u>1H-NMR (CDCl_3)</u>
(101b)	3-biphenyl-4-yl-2-cyano-3-hydroxy-acrylic acid butylester	0.99 (3H, t, $J=7.43$ Hz), 1.45-1.49 (2H, m), 1.74-1.79 (2H, m), 4.36 (2H, t, $J=6.66$ Hz), 7.41 (1H, t, $J=5.89$ Hz), 7.47 (2H, t, $J=6.92$ Hz), 7.62 (2H, d, $J=6.92$ Hz), 7.71 (2H, d, $J=8.71$ Hz), 8.10 (2H, d, $J=8.46$ Hz), 14.27 (1H, s)
(101c)	3-biphenyl-4-yl-2-cyano-3-hydroxy-acrylic acid isobutylester	1.03 (6H, d, $J=6.66$ Hz), 2.07-2.12 (1H, m), 4.13 (2H, d, $J=6.66$ Hz), 7.40 (1H, t, $J=7.30$ Hz), 7.47 (2H, t, $J=7.43$ Hz), 7.62 (2H, d, $J=7.42$ Hz), 7.71 (2H, d, $J=8.20$ Hz), 8.10 (2H, d, $J=8.46$ Hz), 14.27 (1H, s)
1(01d)	3-biphenyl-4-yl-2-cyano-3-hydroxy-acrylic acid octylester	0.89 (3H, t, $J=6.66$ Hz), 1.22-1.45 (10H, m), 1.79 (2H, m), 4.34 (2H, t, $J=6.66$ Hz), 7.40 (1H, t, $J=7.17$ Hz), 7.47 (2H, t, $J=7.17$ Hz), 7.62 (2H, d, $J=7.17$ Hz), 7.71 (2H, d, $J=8.45$ Hz), 8.09 (2H, d, $J=8.45$ Hz), 14.27 (1H, s)
(101e)	3-biphenyl-4-yl-2-cyano-3-hydroxy-acrylic acid 2-ethyl-hexylester	0.85-0.97 (6H, m), 1.25-1.45 (8H, m), 1.72-1.78 (1H, m), 4.24-4.28 (2H, m), 7.40 (1H, t, $J=7.17$ Hz), 7.46 (2H, d, $J=7.30$ Hz), 7.62 (2H, d, $J=7.17$ Hz), 7.71 (2H, d, $J=8.712$ Hz), 8.09 (2H, d, $J=8.45$ Hz), 14.27 (1H, s)
(102a)	2-Cyano-3-[4'-(2-cyano-1-hydroxy-2-octyloxycarbonyl-vinyl)-biphenyl-4-yl]-3-hydroxy-acrylic acid octylester	0.87-0.91 (6H, t, $J=6.92$ Hz), 1.20-1.45 (20H, m), 1.77-1.82 (4H, m), 4.35 (4H, t, $J=6.66$ Hz), 7.75 (4H, d, $J=6.92$ Hz), 8.12 (4H, d, $J=8.46$ Hz), 14.27 (2H, s)
(102b)	2-Cyano-3-[4'-(2-cyano-2-(2-ethyl-hexyloxycarbonyl)-1-hydroxy-vinyl)-biphenyl-4-yl]-3-hydroxy-acrylic acid-2-ethylhexylester	0.9-0.97 (12H, m), 1.30-1.50 (16H, m), 1.71-1.78 (2H, m), 4.20-4.30 (4H, m), 7.75 (4H, d, $J=8.46$ Hz), 8.13 (4H, d, $J=8.46$ Hz), 14.27 (2H, s)
(101f)	2-Cyano-3-hydroxy-3-naphthalen-2-yl-acrylic acid-octyl ester	0.89 (3H, t, $J=6.83$ Hz), 1.20-1.55 (10H, m), 1.75-1.80 (2H, m), 4.35 (2H, t, $J=6.83$ Hz), 7.50-7.60 (2H, m), 7.86 (1H, d, $J=8.29$ Hz), 7.91-7.98 (3H, m), 8.58 (1H, s), 14.27 (1H, s)

Tabelle 2: 13C-NMR data of the compounds

	<u>Compound</u>	<u>13C-NMR (CDCl_3)</u>
(101b)	3-biphenyl-4-yl-2-cyano-3-hydroxy-acrylic acid - butylester	13.81, 19.11, 30.49, 66.66, 78.63, 115.90, 127.11, 128.29, 128.86, 129.06, 129.97, 139.33, 145.91, 171.22, 182.11.

Tabelle 2: ^{13}C -NMR data of the compounds

	<u>Compound</u>	<u>$^{13}\text{C-NMR (CDCl}_3)$</u>
(101c)	3-biphenyl-4-yl-2-cyano-3-hydroxy-acrylic acid -Isobutylester	19.06, 27.80, 72.53, 78.62, 115.83, 127.12, 128.30, 128.87, 129.06, 129.99, 139.34, 145.91, 171.18, 182.10
(101d)	3-biphenyl-4-yl-2-cyano-3-hydroxy-acrylic acid octylester	14.24, 22.75, 25.80, 25.89, 28.50, 29.23, 31.85, 66.97, 78.65, 115.91, 127.12, 128.30, 128.87, 129.06, 129.98, 139.33, 145.91, 171.24, 182.11.
(101e)	3-biphenyl-4-yl-2-cyano-3-hydroxy-acrylic acid -2-ethyl-hexylester	11..09, 14.16, 14.25, 22.79, 23.00, 23.69, 28.94, 29.45, 29.78, 30.23, 31.99, 38.69, 69.00, 78.63, 115.71, 127.06, 128.25, 128.81, 129.03, 129.94, 139.27, 145.83, 171.26, 181.95.
(102a)	2-cyano-3-[4'-(2-cyano-1-hydroxy-2-octyloxycarbonyl-vinyl)-biphenyl-4-yl-3-hydroxy- acrylic acid -octylester	14.25, 22.75, 25.80, 28.49, 29.23, 31.85, 67.08, 79.11, 115.71, 127.33, 129.24, 131.09, 144.05, 171.10, 181.76.
(102b)	2-cyano-3-[4'-(2-cyano-2-(2-ethyl-hexyloxycarbonyl)-1-hydroxy-vinyl)-biphenyl-4-yl-3-hydroxy- acrylic acid -2-ethylhexyl-ester	11.09, 14.16, 22.99, 23.68, 28.93, 30.21, 38.68, 69.11, 79.10, 115.52, 127.28, 129.20, 131.06, 143.97, 171.12, 181.61.

Example 3: Determination of the minimum inhibitory concentration (MIC value)

a) Automatic MIC-Screening according to the broth dilution method:

5

Medium: Casein/soymeal peptone agar (Merck)

Diluent: DMSO

Microorganisms used: *Staphylococcus aureus* ATCC 6538

Escherichia coli ATCC 10536

10

Actinomyces viscosus ATCC 43146

Corynebacterium xerosis ATCC 373 oder

C. minutissimum ATCC 23348

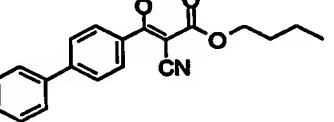
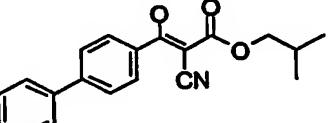
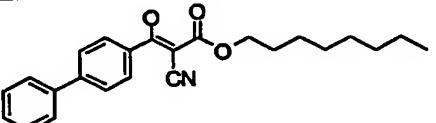
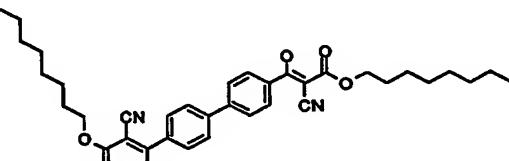
Incubation: 24 to 48 hours at 37°C

Test solution: 0.3 % stock solutions of all the test substances are prepared in a suitable solvent and diluted in serial dilutions to end concentrations of 120 µg/ml to 3.75 µg/ml in DMSO in Deep-Well-plates.

5 Test principle:

8 µl of each dilution step is mixed with 192µl of nutrient medium in micro titer plates. The plates are incubated at 37°C for 24 hours and then the highest dilution (lowest concentration) of the test substance at which growth is just no longer discernible is determined (corresponds to the MIC).

Table 3: MIK in [μm]

<u>Comp. of formula</u>		<u>S. aureus</u>	<u>Corynebacterium sp.</u>	<u>A. viscosus</u>
(101b)		7,5	15	7,5
(101c)		7,5	7,5	7,5
(101d)		<3,75	<3,75	<3,75
(102a)		<3,75	>120	<3,75

b) Determination of MIC vs. different oral germs in the broth dilution method

Medium: Thiglycolate Bouillon with Hemin and Menadion

Columbia Bouillon with Hemin and Menadion für *P. gingivalis*
und *P. nigescens*

5

diluent: the corresponding amount of the substances was pipeted directly

Examples of test

organisms: *Actinobacillus actinomycetemcomitans* ATCC43718

10

Streptococcus gordonii ATCC10558

Streptococcus mutans ATCC33402

Actinomyces viscosus ATCC43146

Fusobacterium nucleatum subsp. *polymorphum* ATCC1095

Porphyromonas gingivalis ATCC3277

15

Prevotella nigescens ATCC33563

Incubation: 7-10 days at 37°C under anaerobic conditions, resp. 24 h aerobically with 10% CO₂ for *Streptococci* und *A. actinomycetemcomitans*

20

Test solution: Stock solutions in ethanol with 1500 ppm (w/w) are used from all test substances

Test principle:

Bacteria are taken from blood agar plates with cotton swabs and a suitable O.D. is adjusted in the corresponding medium (McFarland 0,5). This solution is used for *F. nucleatum* and *P. nigescens* in undiluted state, for the other strains a dilution of 1:20 is used. To each 2 ml of active ingredient containing solution 0.1 ml of the bacteria culture is added and incubated as described above.

The results are listed in Table 4.

Table 4: MHK in [ppm]

	<u>(101b)</u>	<u>(101c)</u>	<u>(101d)</u>	<u>(101e)</u>	<u>(201a)</u>	<u>(201b)</u>
<i>A.actinomycetemcomitans</i> ATCC43718	15	15	≥ 15	>15	> 15	> 15
<i>S. gordonii</i> ATCC10558	3,75	3,75	≤ 0,94	<0,94	15	15
<i>S. mutans</i> ATCC33402	5,63	5,63	≤ 0,94	<0,94	> 15	> 15
<i>A. viscosus</i> ATCC43146	3,75	7,5	≤ 0,94	<0,94	7,5	7,5
<i>F. nucleatum</i> subsp. <i>polymorphum</i> ATCC10953	≤ 0,94	7,5	15	>15	≥ 15	> 15
<i>P. gingivalis</i> ATCC3277	3,75	7,5	7,5	15	> 15	> 15
<i>P. nigrescens</i> ATCC33563	> 15	> 15	> 15	>15	> 15	> 15

c) Determination of MIC for an extended germ spectrum in the Agar incorporation test

Medium: Casein/soymeal peptone agar (Merck)

*Sabouraud 4 % glucose agar (Merck)

Diluent:: Sterile 0.85 % NaCl solution

10	Microorganisms used (examples):	<i>Staphylococcus aureus</i> ATCC 6538 <i>Staphylococcus epidermidis</i> ATCC 12228 <i>Corynebacterium xerosis</i> ATCC 373
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15 **Pseudomonas aeruginosa ATCC 15442**
Candida albicans ATCC 10231 *

Incubation: **24 hours at 37°C**
3 days at 28°C *

Test solution: 1 % stock solutions of all the test substances are prepared in a suitable solvent and diluted in serial dilutions to end concentrations of from 1000 ppm to 10 ppm.

Test principle:

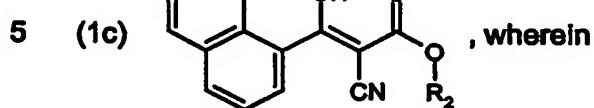
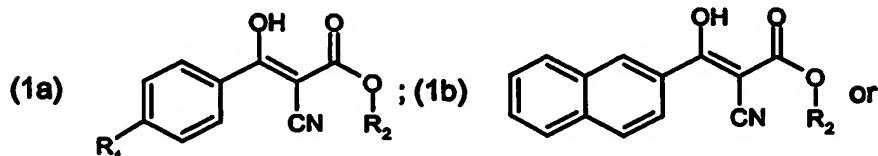
- 5 0.3 ml of each dilution step is mixed with 15 ml of nutrient medium while the latter is still liquid. After the nutrient medium has solidified, 10 µl of each of the following organism dilutions of the test strains in 0.85 % NaCl solution are spotted onto the agar medium.
- 10 The plates are incubated during 24 hours at 37°C and then the highest dilution (lowest concentration) of the test substance at which growth is just no longer discernible (corresponds to the MIC) is determined.

Table 5: MIC in ppm]

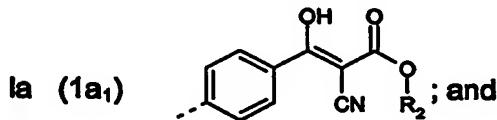
	(101b)	(101c)	(101d)	(101e)	(201b)
<i>Staphylococcus aureus</i> ATCC 6538	6,25	12,5	< 1,56	1,9	100
<i>Staphylococcus epidermidis</i> ATCC 12228	6,25	6,25	< 1,56	1,9	25
<i>Corynebacterium xerosis</i> ATCC 373	3,13	3,13	< 1,56	1,9	< 1,56
<i>C. minutissimum</i> ATCC 23348	12,5	12,5	< 1,56		50
<i>Propionibacterium acnes</i> ATCC 6919	12,5	12,5	6,25	0,94	< 1,56
<i>Escherichia coli</i> ATCC 10536	> 100	> 50	> 400	> 500	> 400
<i>Proteus vulgaris</i> ATCC 6896	> 100	> 50	> 400		> 400
<i>Klebsiella pneumoniae</i> ATCC 4352	> 100	> 50	> 400		> 400
<i>Salmonella choleraesuis</i> ATCC 9184	> 100	> 50	> 400		> 400
<i>Pseudomonas aeruginosa</i> ATCC 15442	> 100	> 50	> 400	> 500	> 400
<i>Candida albicans</i> ATCC 10231	> 100	> 50	> 400	> 500	> 400
<i>Aspergillus niger</i> ATCC 6275	> 100	> 50	> 400		> 400

What is claimed is:

1. 3-aryl-2-cyano-3-hydroxy-acrylsäure derivates of formula



R₁ is hydrogen, C₁-C₂₀alkyl; C₁-C₂₀alkoxy; CF₃; C₆-C₁₀aryl; or a radical of formula-



R₂ is hydrogen; or C₁-C₂₀alkyl.

10 2. Compounds of formula (1a) according to claim 1, wherein

R₁ is C₆-C₁₀Aryl.

3. Compounds according to claim 1 or 2, wherein

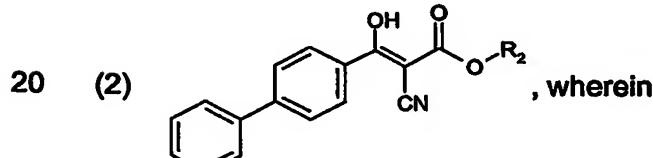
R₁ is phenyl.

15

4. Compounds according to one of claims 1 to 3, wherein

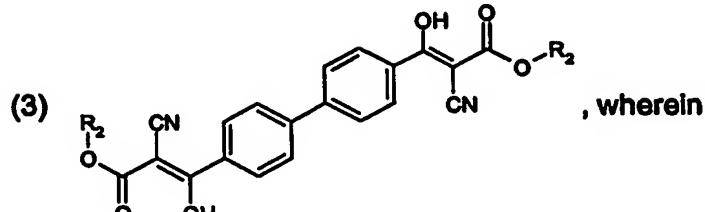
R₂ is C₁-C₂₀alkyl.

5. Compounds according to one of claims 1 to 4, which correspond to formula



R₂ is C₁-C₂₀alkyl.

6. Compounds according to one of claims 1 to 4, which correspond to formula

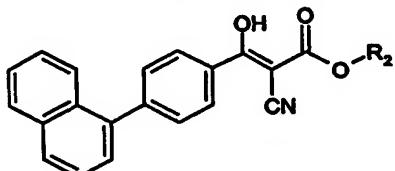
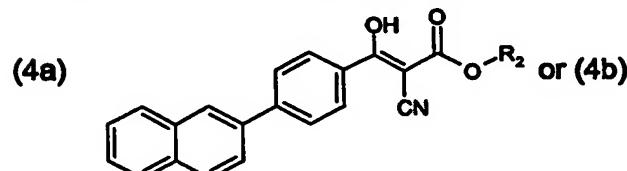


, wherein

R₂ is C₁-C₂₀alkyl.

5

7. Compounds according to one of claims 1 to 4, which correspond to formulae

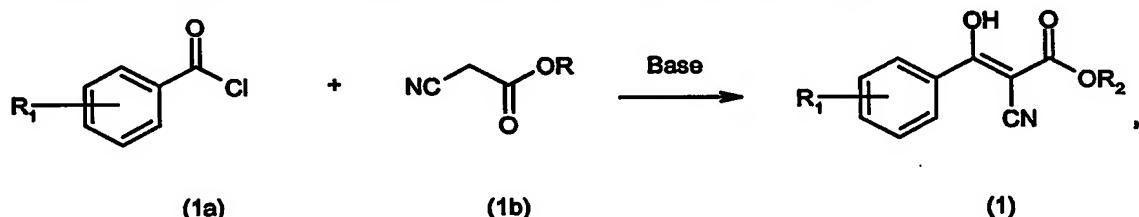


wherein

R₂ is C₁-C₂₀alkyl.

10

8. Process for the preparation of the compounds of formula (1a) according to claim 1, which comprises condensing the cyanoacetate of formula (1a) with the carbon acid chloride of formula (1b) to the compound of formula (1a) according to the following reaction scheme:



15 wherein

R₁ and R₂ are defined as in claim 1.

9. Use of the compounds of formulae (1a), (1b) or (1c) for the antimicrobial treatment of surfaces.

20

10. Use of the compound of formulae (1a), (1b) or (1c) according to claim 9 in the antimicrobial treatment, deodorisation and disinfection of the skin, mucosa and hair.

11. Use according to claim 10, wherein the compound of formulae (1a), (1b) or (1c) are used for the prevention of the adhesion of bacteria on surfaces and the further forming of the biofilmes and for detaching the biofilm and/or for the inhibition of the groth of the biofilm forming microorganisms in the biological matrix or for killing them.

5 12. Use of the compound of formulae (1a), (1b) or (1c) in the treatment of textile fibre materials.

10 13. Use according to claim 9, wherein the compound of formulae (1a), (1b) or (1c) are used in preservation.

14. Use acciording to claim 9, wherein the compound of formulae (1a), (1b) or (1c) are used in washing and cleaning formulations.

15 15. Use according to claim 9, wherein the compound of formulae (1a), (1b) or (1c) are used in imparting antimicrobial properties to, and preserving, plastics, paper, nonwovens, wood or leather.

20 16. Use of the compounds of formulae (1a), (1b) or (1c).In imparting antimicrobial properties to, and preserving, technical products.

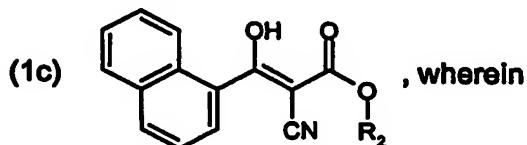
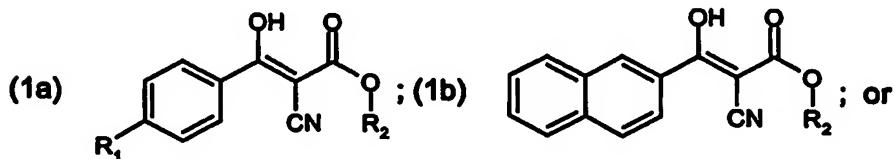
17. Use of the compounds of formulae (1a), (1b) or (1c) as a biocide in technical processes.

**25 18. A personal care preparation comprising
from 0.01 to 15 % by weight, based on the total weight of the composition, of a compound of formulae (1a), (1b) or (1c) and cosmetically tolerable adjuvants.**

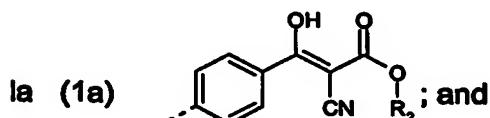
19. An oral composition comprising from 0.01 to 15 % by weight, based on the total weight of the composition, of a compound of formulae (1a), (1b) or (1c), and orally tolerable adjuvants.

Abstract

Disclosed are 3-aryl-2-cyano-3-hydroxy-acrylsäure derivates of formula



R₁ is hydrogen, C₁-C₂₀alkyl; C₁-C₂₀alkoxy; CF₃; C₆-C₁₀aryl; or a radical of formula-



R₂ is hydrogen; or C₁-C₂₀alkyl.

The compounds are used as antimicrobial actives for the treatment of surfaces.

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